42. **(Amended)** The method of claim 41, wherein said [nucleic acid comprises a viral vector, said] delivery agent comprises a virus particle including said nucleic acid.

47. **(Amended)** A coacervate microsphere for transfection and expression of a recombinant protein prepared by the process comprising:

a. in any order:

i. adding a cationic molecule to a first aqueous solution;

ii. adding a anionic molecule to a second aqueous solution; and,

iii. adding to either said first or said second solution a virus comprising a viral vector comprising a nucleic acid encoding a recombinant protein and at least one regulatory element;

b. mixing said first and second solution together to form a coacervate microsphere of said cationic molecule and said anionic molecule encapsulating said virus; and,

c. isolating said coacervate microspheres,

wherein said coacervate releases said virus *in vivo* or *in vitro*, whereby said virus transfects cells, resulting in expression of said recombinant protein.

Remarks

Claims 1-2 and 4-49 constitute the pending claims in the present application. Claims 8, 17, 24, 26, 29, 30, 32, 37, 41, 42, and 47 have been amended. Support for the claim amendments can be found throughout the specification. No new matter has been added.

Amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note with appreciation the entry of the previous Response and the subsequent withdrawal of rejections based on 35 U.S.C. 102, 103, and 112, second paragraph.

Regarding the rejection of claims 1-15, 21, 23-28, 36, 37, and 39-47 under 35 U.S.C. 102(a) that was maintained by the Examiner because the Patent Office has allegedly not received the Declaration under 37 C.F.R. 1.132, Applicants are submitting a signed and dated Declaration herewith. Accordingly, withdrawal of this rejection is respectfully requested.

Specification

Applicants submit herewith a substitute specification to correct the improper margins of the specification as originally filed. I hereby state that this substitute specification is identical in content to the originally filed specification; accordingly, the substitute specification contains no new matter, and no marked-up copy is being filed. Applicants point out that the amendment to the Abstract on page 69 made in the previous response has not been entered into the substitute specification. Moreover, the substitute specification contains the claims as originally filed.

Double Patenting

Claims 25 and 26 are rejected as being substantial duplicates of each other. However, a "transgene," recited in claim 25, does not have to encode a recombinant protein. For example, a transgene could encode an antisense RNA (see the definition of "transgene" at page 7, which does not limit the scope of "transgene"). Accordingly, Applicants submit that claims 25 and 26 are directed to different subject matter. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claims 29-34, 38, and 48 under 35 U.S.C. 112, first paragraph

Claims 29-34, 38, and 48 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Applicants respectfully traverse this rejection.

The Examiner states that the evidence provided by the Applicants "can not be extrapolated to the instantly claimed invention which when read in light of the specification is drawn to methods of delivering a nucleic acid to a host or the sustained release of a virus to a target site presumably in a host and a gene delivery system for transducing cells of a host or for transfecting a cell with a viral vector for the purposes of gene therapy and nucleic acid immunization." The Examiner states that "Applicants fail to enable the use of methods for delivering a nucleic acid to a host and a gene delivery system for gene therapy and genetic immunization."

Claims 29 and 30 have been amended by removing the reference to a host, since the claimed coacervates can also be used in *ex vivo* and *in vitro* deliveries of nucleic acids.

Claim 48 is drawn to a delivery system for transfecting a cell with a viral vector. Applicants note that the cell does not have to be in a host.

Applicants respectfully reiterate that the asserted utilities of gene therapy and genetic immunization were credible to a person of skill in the art at the time the application was filed, and that the specification provides sufficient details that would enable a person of skill in the art to use the claimed coacervates for delivering genes into a subject. At the time the application was filed, numerous clinical trials were ongoing in which DNA was introduced into subjects. Furthermore, many companies existed that had been formed to develop gene therapy techniques. Thus, even if some more experimentation may be necessary for developing certain gene therapy protocols, the evidence shows that a person of skill in the art at the time the application was filed would have found gene therapy is credible.

Applicants note that a gene delivered using the claimed invention does not necessary have to encode a protein which cures a disease, but can also encode a toxin for killing undesirable cells (see, e.g., page 40, line 7). Alternatively, the protein encoded by the gene introduced into a subject could be a marker, such as for *in vivo* labeling of cells ("imaging" use, see, e.g., page 5, line 28). Such toxins and markers were well known in the art at the time the application was filed. The specification teaches that the coacervates can be injected into a target site, e.g., a tumor (see, e.g., page 58, lines 8-10). Furthermore, as acknowledged by the Examiner, Applicants have provided a working example showing that introduction of the claimed coacervates into a tumor in a nude mice results in expression of the nucleic acid introduced. Accordingly, the specification and the general knowledge in the art at the time the invention was made provided sufficient teachings to enable a person of skill in the art to administer to a subject the claimed coacervates and obtain the desired results.

In addition, the specification provides uses for the claimed invention other than gene therapy and genetic immunization. For example, the specification teaches that the coacervates of the invention can also be used for diagnosis (page 5, line 28). The specification further states that the coacervates can also be used *in vitro* (see, e.g., page 36, line 9 and page 43, lines 15-16). In particular, a person skilled in the art would recognize that any protein that one wishes to produce *in vitro* in a eukaryotic cell (e.g., for use in an antigen vaccine) can be produced from a cell that has been contacted with a coacervate comprising a nucleic acid encoding the protein. The invention can also be used in an *ex vivo* gene therapy protocol (page 38, line 15). Thus, the invention can generally be used in any application in which it is desirable to introduce DNA or a virus into a cell. A person of skill in the art would also recognize that the claimed invention using a virus encapsulated in a coacervate microsphere can be used as a vaccine, for inducing an

immune response against the virus. Accordingly, since the invention provides a least one method of using the claimed invention that is commensurate with the scope of the claims, the claimed invention meets the 112, first paragraph requirement of teaching how to make and use the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 29-34, 38, and 48 under 35 U.S.C. 112, first paragraph.

Rejection of claims 17-20, 22, 35, and 39-47 under 35 U.S.C. 112, first paragraph

Claims 17-20, 22, 35, and 39-47 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Applicants respectfully traverse this rejection.

The Examiner acknowledges that the specification is "enabling for the composition of a controlled release of a nucleic acid of the instant invention, a method for preparing the same, a coacervate microsphere for transfection and expression of a recombinant protein *in vitro*, and a kit comprising microspheres and instructions for using said microspheres."

As set forth above, in the discussion addressing the rejection of claims 29-34, 38, and 48 under 35 U.S.C. 112, first paragraph, the claimed coacervates can be used for both *in vivo* and *in vitro* uses. When used *in vivo*, the coacervates can be injected into a host. Applicants have demonstrated that a nucleic acid introduced into a tumor via coacervates of the invention is properly expressed in cells of the tumor, demonstrating that the coacervate efficiently delivered expressible DNA to a target cell. Since the claims do not require a therapeutic effect, and since the specification provides *in vivo* uses which do not require a therapeutic effect (e.g., "imaging"), it is not necessary for Applicants to demonstrate that a therapeutic effect results from administration of the coarcervate in the animal model.

As further set forth above, the specification provides for *in vitro* uses of the claimed invention. Thus, since the invention provides a least one method of using the claimed invention that is commensurate with the scope of the claims, the claimed invention meets the 112, first paragraph requirement of teaching how to make and use the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 17-20, 22, 35, and 39-47 under 35 U.S.C. 112, first paragraph.

Rejection of claims 8, 9, 17-20, 22, 24, 37, 40, 42, 44, and 47 under 35 U.S.C. 112, second paragraph

Claims 8, 9, 17-20, 22, 24, 37, 40, 42, 44, and 47 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended claim 8 to provide antecedent basis for the term "said crosslinking agent" by making this claim dependent on claim 7.

Applicants have amended claim 17 to clarify that the recited limitation is a characteristic of the microsphere, and not a method step.

Regarding claims 24 and 31, although Applicants submit that these claims are sufficiently clear in their unamended form in view of the specification. The term "vector" is used in the specification to refer to a nucleic acid. However, merely for expediting prosecution of this application, Applicants have amended claim 24 for purposes of clarity.

Although Applicants assert that one of skill in the art would recognize that a natural virus engineered to be used as a vector" is not necessarily identical to a recombinant virus, Applicants have amended claim 37 to remove the phrase "natural virus which has been engineered to be used as a vector" to overcome the Examiner's objection.

Applicants have interpreted the rejection of claims 40 and 44 as a rejection of claims 41 and 44. Applicants have amended claim 41 to more particularly point out the subject matter being claimed. With respect to claim 44, Applicants submit that the term 'substantially aqueous' would be understood by one of skill in the art based on the synthesis procedure on page 57 of the substitute specification, in light of the knowledge in the art which would guide the skilled artisan towards the selection of solutions that are sufficiently aqueous to permit preparation of coacervates as described in the instant specification. The term 'substantially' was found to be definite in *In re Mattison*, 184 USPQ 484 (CCPA 1975) in view of the general guidelines in the specification, and in *Andrew Corp. v. Gabriel Electronics*, 6 USPQ2d 2010 (Fed. Cir. 1988) because one of skill in the art would have understood what was meant by the term "substantially equal." Applicants submit that the guidance of the specification and the level of skill in the art indicate that the term 'substantially' in the context of claim 44 would similarly be definite to one of skill in the art.

Applicants have amended claim 42 to clarify the subject matter being claimed.

Applicants have amended claim 47 to more particularly point out that the limitation objected to by the Examiner reflects a characteristic of the claimed composition, rather than a method step.

For the reasons set forth above, Applicants submit that the pending claims, as amended, fully comply with 35 U.S.C. 112, second paragraph. Reconsideration and withdrawal of these rejections is respectfully requested.

Rejection of claims 1, 2, 4, 5, 7, 11, 13, 14 and 15 under 35 U.S.C. 102(e)

Claims 1, 2, 4, 5, 7, 11, 13, 14, and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Truong et al., U.S. Patent No. 6,025,337. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

A claim is anticipated by a reference only if the reference teaches each and every element of the claim. It is the Examiner's position that "Truong et al. disclose[s] a solid microparticle or microsphere (column 7, line 8) for delivering of nucleic acid to and transfection of target cells comprising gelatin (cationic molecule), nucleic acid, chondroitin sulfate (anionic molecule), wherein a molecular species (delivering agent) is attached to the surface of the microparticle, wherein the molecular species is selected from the group consisting of a targeting ligand and a linking molecule." Applicants respectfully submit that Truong et al. does not teach a "delivery agent incorporated in the coacervate," as required by claim 1 and claims 2, 4, 5, 7, 11, 13, 14 and 15 dependent therefrom. A "delivery agent" is defined in the specification as "a molecule that facilitates the intracellular delivery of a bioactive substance" (page 9, lines 5-6). The specification further provides that exemplary delivery agents include viruses or virus particles, such as an adenoviral vector, an adeno-associated viral vector or a retroviral vector (page 5, lines 7-9); sterols or lipids (page 5, line 17); cationic liposomes (lipofectin), polylysine conjugates, polyarginine, bisguanidine cholesterol, artificial viral envelopes and other like intracellular carriers (page 27, lines 15-17); and amphiphilic compounds (page 31, line 21).

In addition, Truong et al. teaches a gene delivery system made of gelatin and nucleic acids. Although Truong et al. state that "[c]hondroitin sulfate can also be added into the microparticle," Truong et al. does not teach or suggest that gelatin and chondroitin sulfate form a coacervate that also incorporates a nucleic acid and a delivery agent. On the contrary, Truong et al. rely on the interaction between negatively charged DNA and the positively charged cations in order to achieve coacervation (col. 3, lines 16-19).

Accordingly, since Truong et al. fail to teach each and every element of claim 1 and dependent claims 2, 4, 5, 7, 11, 13, 14, and 15, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claims 1, 2, 4, 6, 16, 23-28 and 35 under 35 U.S.C. 103(a) as being unpatentable over Truong et al. in view of Beer et al.

Claims 1, 2, 4, 6, 16, 23-28, and 35 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Truong et al. (U.S. Patent No. 6,025,337) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997). Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Examiner relies on Truong et al. as "disclosing a solid microparticle or microsphere [...] for delivering of nucleic acids to and transfection of target cells comprising gelatin (cationic molecule), nucleic acid, chondroitin sulfate (anionic molecule), wherein a molecular species (delivering agent) is attached to the surface of the microparticle." The Examiner also relies on Truong et al. as teaching that "microspheres can be synthesized by the coacervation of gelatin and chondroitin sulfate." The Examiner acknowledges that "Truong et al. did not teach specifically the incorporation of a recombinant virus into the disclosed microparticle or microsphere or a kit comprising the same."

The Examiner relies on Beer et al. as disclosing "a composition of poly (lactic-glycolic) acid (PLGA) microspheres containing a recombinant adenovirus."

The Examiner states that "it would have been obvious to a person of skill in the art at the time the invention was made to modify a microsphere composition disclosed by Truong et al. by replacing a plasmid vector with a recombinant adenovirus taught by Beer et al. to arrive at the instant claimed invention." Applicants respectfully submit that the combination of the teachings of the two references does not result in the claimed invention. Truong et al. teach coacervates between a nucleic acid and gelatin. If, as suggested by the Examiner, a microsphere disclosed by Truong et al. is modified by replacing the plasmid vector with a recombinant adenovirus taught by Beer et al., a coacerate would probably not form because the nucleic acid of the recombinant virus is in a viral particle. Furthermore, even if such a coacerate did form, it would comprise only gelatin and the recombinant adenovirus of Beers et al. Even if Truong et al. state that "[c]hondroitin sulfate can also be added into the microparticle," Truong et al. does not teach or suggest that the addition of chondroitin sulfate to gelatin and a nucleic acid and a delivery agent, e.g., a virus, would form a coacervate that incorporates a nucleic acid and a delivery agent. Accordingly, the combination of the teachings of the two references does not meet all the claim limitations, and there would not have been a reasonable expectation of success or sufficient motivation to combine the cited references to arrive at the claimed composition.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 2, 4, 6, 16, 23-28, and 35 under 35 U.S.C. 103(a) as unpatentable over Truong et al. in view of Beer et al. is respectfully requested.

Rejection of claims 1 and 49 under 35 U.S.C. 103(a) as being unpatentable over Truong et al. in view of Casey et al.

Claims 1 and 49 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Truong et al. (U.S. Patent No. 6,025,337) in view of Casey et al. (Oncogene 6:1791-1797, 1991) Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

It is the Examiner's position that "Truong et al. did not teach an incorporation of a plasmid vector containing a DNA sequence encoding a polypeptide that inhibits cell proliferation," but that, "the claimed invention would have been obvious since one of ordinary skilled in the art would have replaced the plasmid vector disclosed by Truong et al. with one taught by Casey et al. for inhibiting certain cancer cell populations having mutated p53." Applicants respectfully submit that the combination of the teachings of the two references does not result in the claimed invention. Truong et al. teach coacervates between a nucleic acid and gelatin. If, as suggested by the Examiner, the plasmid vector disclosed by Truong et al. is replaced with one taught by Casey et al., the result would be a coacervate comprising gelatin and the plasmid of Casey et al. Even if Truong et al. state that "[c]hondroitin sulfate can also be added into the microparticle," Truong et al. does not teach or suggest that the addition of chondroitin sulfate to gelatin and a nucleic acid and a delivery agent, e.g., a virus, would form a coacervate that incorporates a nucleic acid and a delivery agent. Accordingly, the combination of the teachings of the two references does not meet all the claim limitations, and there would not have been a reasonable expectation of success or sufficient motivation to combine the cited references to arrive at the claimed composition.

Accordingly, reconsideration and withdrawal of the rejection of claims 1 and 49 under 35 U.S.C. 103(a) as unpatentable over Truong et al. in view of Casey et al. is respectfully requested.

Rejection of claims 40-47 under 35 U.S.C. 103(a) as being unpatentable over Leong et al. in view of Truong et al. and Beer et al.

Claims 40-47 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Leong et al. (U.S. Patent No. 5,759,582) in view of Truong et al. (U.S. Patent No. 6,025,337) and Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997). Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Examiner relies on Leong et al. as teaching "a method for preparing a pharmaceutical composition in the form of microspheres, comprising the following steps: (a) providing a gelatin (a cationic molecule) aqueous solution; (b) providing a chondroitin sulfate (an anionic molecule) aqueous solution; (c) adding a therapeutically effective amount of a

pharmaceutically active substance either to the solution in step (a) or to the solution in step (b); (d) mixing the gelatin and chondroitin sulfate solutions to form a coacervate suspension; (e) adding a crosslinking agent [...]; and (f) incubating the coacervate suspension to form microspheres." The Examiner acknowledges that "Leong et al. did not teach a process for preparing a coacervate microsphere which encapsulates a nucleic acid."

The Examiner relies on Truong et al. as disclosing "a solid [...] microsphere [...] for delivering of nucleic acids to and transfection of target cells comprising gelating (cationic molecule), nucleic acid, chondroitin sulfate (anionic molecule), wherein a molecular species (delivering agent) is attached to the surface of the microparticle" and that "microspheres can be synthesized by the coacervation of gelatin and chrondroitin sulfate." The Examiner acknowledges that "Truong et al. did not teach specifically the incorporation of a recombinant virus into the disclosed microparticle or microsphere."

The Examiner relies on Beer et al. as "disclosing a composition of poly (lactic-glycolic) acid (PLGA) microspheres containing a recombinant adenovirus."

The Examiner states that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify a method of preparing a coacervate microsphere disclosed by Leong et al. with the combined teachings of Truong et al. and Beer et al., by substituting a pharmaceutical composition comprising water soluble protein, peptide, glycoprotein, or mixture thereof in step (c) with a recombinant adenovirus to arrive at the instantly claimed invention, including a coacervate microsphere prepared by the same process." Applicants respectfully submit that the cited references, even if combined with the general knowledge in the art at the time the invention was filed, fail to provide sufficient motivation to combine them. In addition, there would have been no reasonable expectation of success to obtain the claimed invention by combining the cited references. The Examiner relies on Truong et al. as teaching that a nucleic acid can be delivered by a microsphere prepared from the coacervation of a cationic molecule and an anionic molecule. The Examiner then relies on Beer et al. as teaching the incorporation of a recombinant virus into a microsphere. However, as discussed above, even if, as suggested by the Examiner, a microsphere disclosed by Truong et al. is modified by replacing the plasmid vector with a recombinant adenovirus taught by Beer et al., a coacervate would probably not form because the nucleic acid of the recombinant virus is in a viral particle. Furthermore, even if such a coacervate did form, it would comprise only gelatin and the recombinant adenovirus of Beers et al. In addition, even if Truong et al. state that "[c]hondroitin sulfate can also be added into the microparticle," Truong et al. does not teach or suggest that the addition of chondroitin sulfate to gelatin and a nucleic acid and a delivery agent, e.g., a virus, would form a coacervate that incorporates a nucleic acid and a delivery agent. Thus, even if combined with Leong et al., there would not have been sufficient motivation to

combine the cited references, nor a reasonable expectation of success to obtain the claimed invention.

Accordingly, reconsideration and withdrawal of the rejection of claims 40-47 under 35 U.S.C. 103(a) as unpatentable over Leong et al. in view of Truong et al. and Beer et al. is respectfully requested.

Rejection of claims 1, 2, 4, 8, 9, 10, 12, 21, 36, and 37 under 35 U.S.C. 103(a) as allegedly being unpatentable over Leong et al. in view of Truong et al. and Beer et al. and Watts et al.

Claims 1, 2, 4, 8, 9, 10, 12, 21, 36, and 37 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Leong et al. in view of Truong et al. and Beer et al., further in view of Watts et al. WO 98/30207. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Examiner relies on Leong et al., Truong et al. and Beer et al., as discussed above. The Examiner states that "they do not suggest the formation of a coacervate microsphere wherein the anionic molecule is alginate and the cationic molecule is gelatin, and wherein the microsphere is crosslinked by a calcium metal ion." The Examiner relies on Watt et al. as teaching "the production of microspheres by complexation between a negatively charged material such as alginate and a postively charged chitosan in the presence of calcium ion." The Examiner states that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to further modify the coacervate microspheres resulted from the combined teachings of Leong et al., Truong et al. and Beer et al. for substituting chondroitin sulfate for alginate, and using calcium as a crosslinking agent to arrive at the instant claimed invention." Applicants respectfully submit that, as discussed above, there would not have been sufficient motivation to combine Leong et al., Truong et al. and Beer et al., nor a reasonable expectation of success to obtain the claimed invention. Thus, it would not have been obvious for a person of skill in the art to substitute chondroitin sulfate for alginate and to use calcium as a crosslinking agent to arrive at the instant claimed invention.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 2, 4, 8, 9, 10, 12, 21, 36, and 37 under 35 U.S.C. 103(a) as unpatentable over Leong et al. in view of Truong et al. and Beer et al. is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-832-1000.

Respectfully Submitted,

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Copy of the amended claims with changes marked thereon

8. **(Amended)** The composition of claim [4] 7, wherein said crosslinking agent comprises a metal cation.

17. **(Amended)** The composition of claim 15, wherein [administration of] said microsphere, when administered to a patient, provides [results in] controlled release of said expression vector.

24. **(Twice Amended)** The composition of claim 2, wherein [said nucleic acid is a viral vector, and] said delivery agent is a virus of said viral vector.

26. **(Amended)** The composition of claim 24, wherein said viral vector contains a nucleic acid encoding a recombinant gene product.

29. **(Amended))** A gene delivery system for transducing cells [of a host], comprising: a coacervate microsphere encapsulating at least a nucleic acid and a delivery agent for facilitating intracellular delivery of said nucleic acid, wherein upon [administration] contact of cells with said coacervate microsphere [to a host], controlled release of said nucleic acid results in transduction of the cells [of said host] by said nucleic acid.

30. **(Amended)** A method for delivering a nucleic acid [to a host] into a cell, comprising: [administering to a host] contacting a cell with a composition comprising a coacervate, wherein:

i. said coacervate incorporates a nucleic acid contained in a transfer vector having at least one regulatory element;

ii. said coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid;

iii. said coacervate is a microsphere; and,

iv. said coacervate incorporates a delivery agent,

wherein said [administration] contacting of a cell with said composition results in controlled release of said transfer vector in [vivo] the cell.

32. **(Amended)** The method of claim 31, wherein the nucleic acid encodes a therapeutic agent, the cells are in [the] a host and are transfected with the nucleic acid and express the therapeutic agent, and said agent produces a therapeutically beneficial response in said host.

37. **(Twice Amended)** The coacervate microsphere of claim 36, wherein said virus comprises a recombinant virus [or a natural virus which has been engineered to be used as a vector].

41. **(Amended)** The method of claim 40, wherein [substantially all of] said coacervates [are] consist essentially of microspheres.

42. **(Amended)** The method of claim 41, wherein said [nucleic acid comprises a viral vector, said] delivery agent comprises a virus particle including said nucleic acid [corresponding to said viral vector, and said viral vector is encapsulated in said virus particle].

47. **(Amended)** A coacervate microsphere for transfection and expression of a recombinant protein prepared by the process comprising:

a. in any order:

i. adding a cationic molecule to a first aqueous solution;

ii. adding a anionic molecule to a second aqueous solution; and,

iii. adding to either said first or said second solution a virus comprising a viral vector comprising a nucleic acid encoding a recombinant protein and at least one regulatory element;

b. mixing said first and second solution together to form a coacervate microsphere of said cationic molecule and said anionic molecule encapsulating said virus; and,

c. isolating said coacervate microspheres,

wherein [release of said virus from] said coacervate [and transfection of cells by] releases said virus *in vivo* or *in vitro*, whereby said virus transfects cells, resulting [results] in expression of said recombinant protein.